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SEARCH FOR RADIOPROTECTIVE COMPOUNDS. PART XIX. PROTECTION PROV--ETC(U)
OCT 80 G A GRANT, K E LEACH

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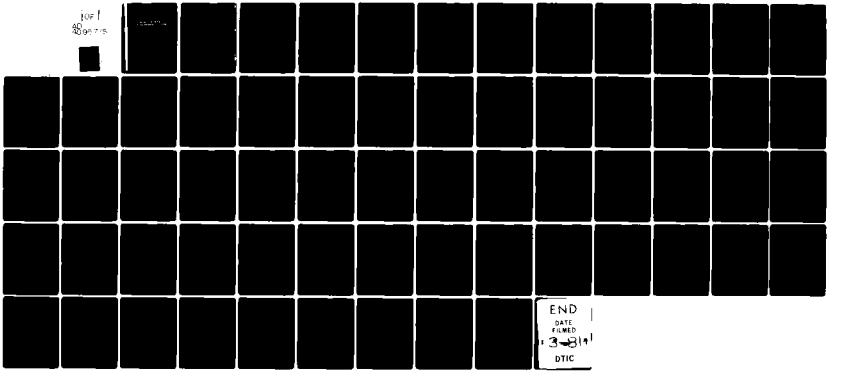

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DREO REPORT NO. 827
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SEARCH FOR RADIOPROTECTIVE COMPOUNDS PART XIX

PROTECTION PROVIDED TO MICE BY ORAL ADMINISTRATION OF LIPID– AND WATER-SOLUBLE COMPOUNDS

by

G.A. Grant and Karen Leach

OCTOBER 1980
OTTAWA

CAUTION

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SEARCH FOR RADIOPROTECTIVE COMPOUNDS.

PART XIX •

PROTECTION PROVIDED TO MICE BY ORAL ADMINISTRATION OF LIPID– AND WATER-SOLUBLE COMPOUNDS

by
G.A. Grant and Karen Leach
Protective Sciences Division
Radiation Biology Section

OCTOBER 1988
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ABSTRACT

Forty-two compounds previously screened at the Walter Reed Army Institute of Research were selected for further evaluation. The compounds were administered orally to mice prior to gamma irradiation. The $LD_{50/30}$ was computed and dose reduction factors determined. Dose reduction factors up to 1.45 were obtained for both water- and lipid-soluble compounds with administered oral doses of 100 mg/kg or less. The relationship between chemical structure and protective activity of the compounds is discussed.

RÉSUMÉ

Quarante-deux composés, examinés préalablement à l'Institut de recherches Walter Reed de l'armée, ont été retenus pour des études plus approfondies. On les a administrés par voie orale à des souris, avant irradiation par rayonnement gamma. Les $DL_{50/30}$ ont été calculées par ordinateur, et on a déterminé les facteurs de réduction de dose. Les valeurs obtenues pour ces derniers allaient jusqu' à 1.45, qu'il s'agisse de composés solubles dans l'eau ou bien dans les lipides, et ce à des doses orales de 100 mg/kg ou moins. On examine la relation entre la structure chimique et l'activité protectrice de ces composés.

Protection Provided to Mice by Oral Administration of Lipid- and Water-Soluble Compounds

INTRODUCTION

One of the objectives in the program on chemoprophylaxis against ionizing radiation is to synthesize compounds which provide protection when administered orally. For a 70-kilogram man it is desirable that the compounds should be effective when given in a dose of approximately 50 mg/kg or less to avoid administering numerous tablets.

The principal achievement of the program until a few years ago was the development of compounds which provide dose reduction factors up to 2.5 when administered intraperitoneally to mice or intravenously to larger animals and have fewer side effects than the previously synthesized thiols and disulphides (1,2). Unfortunately their protective activity is greatly reduced when given orally, and the dose reduction factor only approaches 1.5 when very large doses are administered.

It was thought that the poor oral absorption was due to the charged groups attached to the sulphur atom in the compounds and lack of lipid solubility. Efforts were made at the Walter Reed Army Institute of Research (WRAIR) during the last four or five years of the large United States development program on radioprotectors, as well as in other countries, to synthesize radioprotective agents with increased lipid solubility and fewer charged chemical groups.

Preliminary biological screening using oral administration at WRAIR resulted in some promising leads. When the WRAIR program came to a premature halt it was decided as part of the DREO program to select a number of their compounds which showed promise in providing protection by the oral route and obtain quantitative data useful in designing more effective compounds for oral administration. In this study approximately forty compounds with various chemical structures, conferring different lipid- and water- solubility properties, were chosen from the preliminary screening data and dose reduction factors determined.

EXPERIMENTAL

Biological Assays

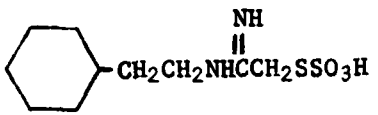
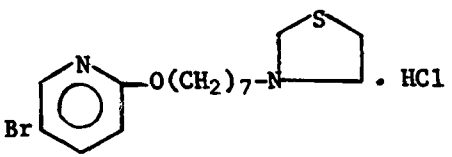
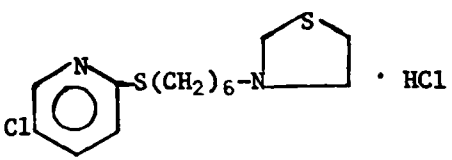
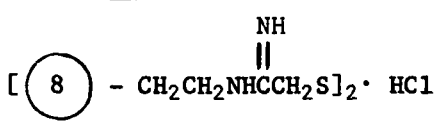
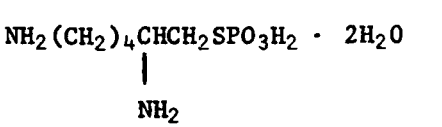
The water-soluble compounds were dissolved in pH 7.2 phosphate buffer and given orally by use of a round-tipped hypodermic needle. The lipid-soluble compounds were dissolved in CMCTW (0.3% carboxymethyl cellulose-0.1% Tween 80) and administered as above. The mice were from Bio-Breeding Laboratories, Ottawa, and were SPF COBS white females weighing 25 to 28g. They were irradiated in a special Caesium 137 irradiator at a dose rate of 85.1 rads/min. (3). The mice were maintained five per cage in wire-bottomed cages in an air-conditioned room. An automatic chlorinated drinking water system was employed to avoid the use of drinking-water bottles. To determine the $LD_{50}/_{30}$, 5 to 6 groups, each containing twenty mice were given graded doses of radiation and dead mice were counted daily during a thirty-day period. Since from past experience it was found that control values for untreated mice did not change greatly from month to month, control curves were done once every three weeks and a group of twenty untreated mice were irradiated with each day's treated mice. The $LD_{50}/_{30}$ and other statistical parameters were calculated with the aid of a computer program for probit analysis. The dose reduction factors (DRF) were calculated if the slopes of response curves for untreated and treated groups were approximately parallel:

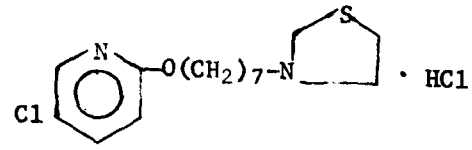
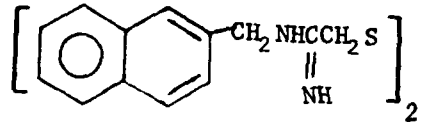
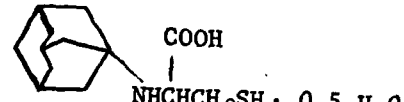
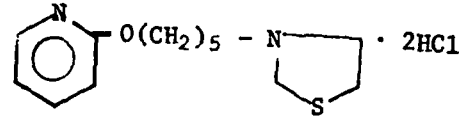
$$DRF = \frac{LD_{50}/_{30} \text{ (Treated)}}{LD_{50}/_{30} \text{ (Untreated)}}$$

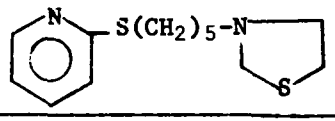
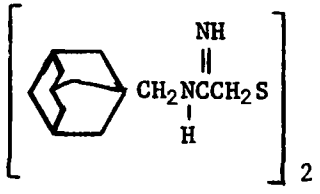
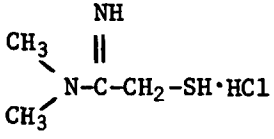
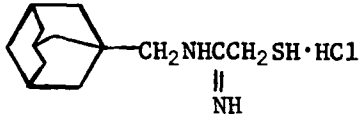
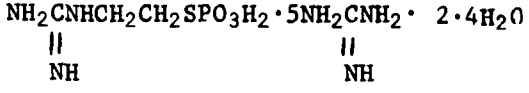
If the probit lines were not parallel the DRF value is quoted as an approximate value.

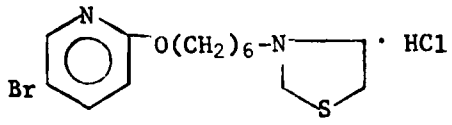
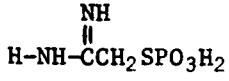
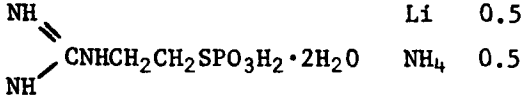
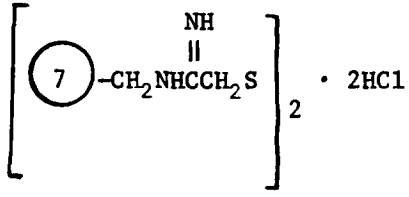
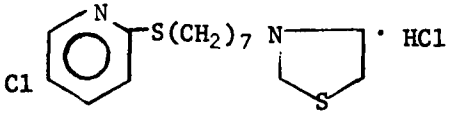
Materials

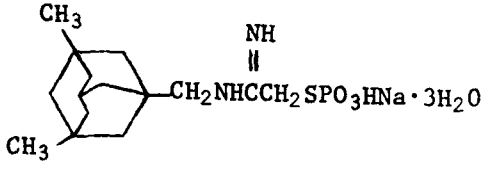
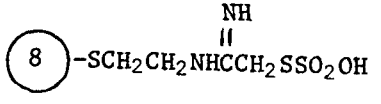
The compounds were received from WRAIR or, in cases where a sufficient amount was not available, resynthesized by the Ontario Research Foundation under contract from Defence Research Establishment Ottawa. The compounds studied are listed below:

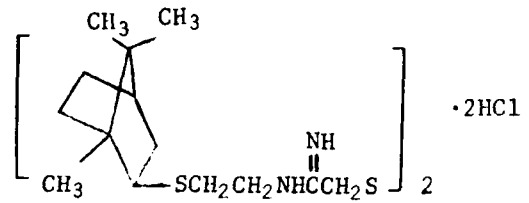
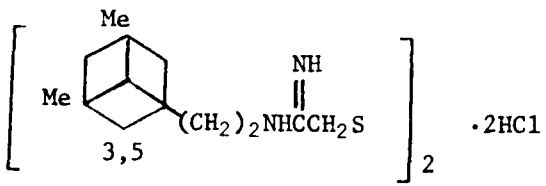
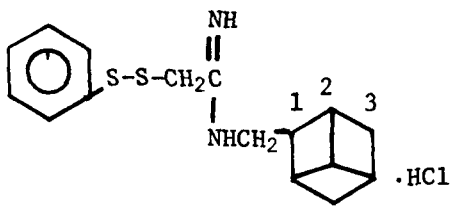
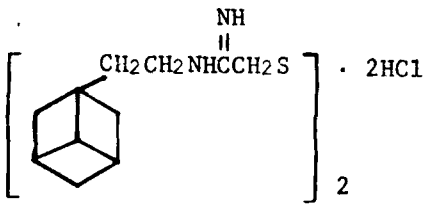
Compound No.	Compound Structure	Compound Name	WR No.
1.		S-[N-(2-cyclohexylethyl) carboxamidinomethyl] thiosulfuric acid	4245AB
2.		5-Bromo-2-[7-(3-thiazolidinyl)-heptyloxy]pyridine-hydrochloride	144975AB
3.		5-Chloro-2-[6-(3-thiazolidinyl)-hexylthio]pyridine hydrochloride	132194AG
5.		S(N-2-cyclooctyethyl)carboxamidino methyl disulfide dihydrochloride	199740AA
7.		S-2,6-Diaminohexyl dihydrogen phosphorothioate dihydrate	176542

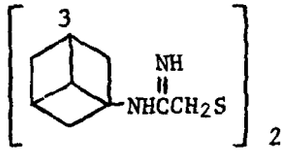
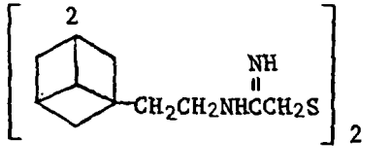
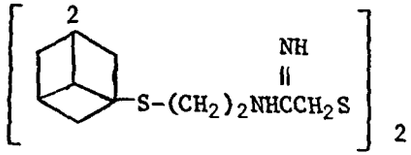
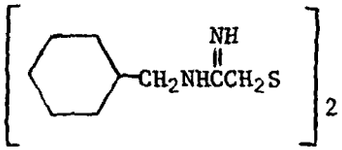
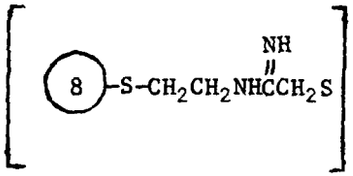
Compound No.	Compound Structure	Compound Name	WR No.
8.		5-Chloro-2-[7-(3-thiazolidinyl)-heptyloxy]pyridine hydrochloride	144976AA
9.		S(N-naphthylmethyl)carboxamidino methyl disulfide dihydrochloride	197486AA
11. 38.		N-(2-adamantyl)cysteine hemihydrate	190205AB
14		5-Bromo-2-[5-(3-thiazolidinyl)-pentoxy]pyridine dihydrochloride	43898AD

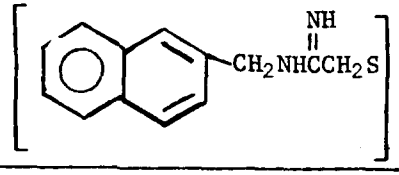
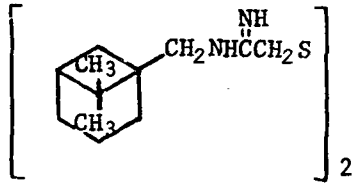
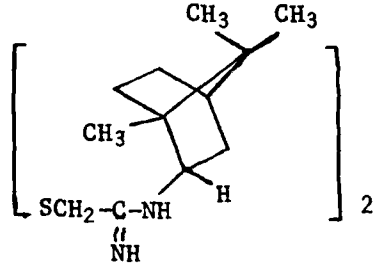
Compound No.	Compound Structure	Compound Name	WR No.
15.		5-Chloro-2-[5-(3-thiazolidinyl-pentylthio]pyridine dihydrochloride	126455AB
16. 27.		S(N-adamantylmethyl)carboxamidino methyl disulfide dihydrochloride	155419AB
20.		N-dimethyl mercaptoacetamidine hydrochloride	76841AB
21. 45.		N-(adamantylmethyl)mercapto-acetamidine hydrochloride	109342AC
23.		S-2-Guanidinoethyl guanidinium hydrogen phosphorothioate hydrate	176240AB

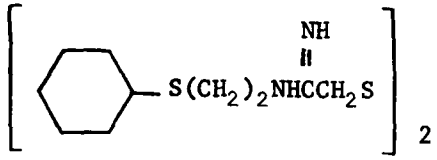
Compound No.	Compound Structure	Compound Name	WR No.
24.		5-Bromo-2-[6-(3-thiazolidinyl)-hexyloxy]pyridine hydrochloride	91496AD
25.	$CH_3NHCH_2CH_2CH_2NH(CH_2)_2SPO_3H_2$	S-2-[3-(methylamino)propyl-amino]ethyl dihydrogen phos-phorothioate	3689AD
17. 26.		S-Acetamidinethiophosphoric acid	108250AB
30.		Mixed lithium ammonium salt of S-(2-guanidinoethyl)dihydrogen phosphorothioate monohydrate	180152
34.		2,2'-Dithiobis-[N-(cycloheptyl-methyl)acetamidine] dihydrochloride	151331AB
36.		5-Chloro-2[7-(3-thiazolidinyl) heptylthio]pyridine hydrochloride	158490AB

Compound No.	Compound Structure	Compound Name	WR No.
32.		Sodium hydrogen-S[N-3,5-dimethyl (1-adamantane methyl)carboxy amidino]methyl phosphorothioate hydrate	159243AB
33.	$NH_2CCH_2SSO_3H$ $\parallel$ NH	α-Acetamidinothiosulphuric acid	1551AD
35.	$\left[\begin{array}{l} NH_2CCH_2S \\ \parallel \\ NH \end{array} \right]_2 \cdot 2HCl$	Carboxamidine methyl disulfide dihydrochloride	33763AD
13.	$NH_2(CH_2)_4CHCH_2SPO_3H_2 \cdot 2H_2O$ (Li) $\vert$ NH_2	L/$^+$/S-2,6-Diaminohexyl dihydrogen phosphorothioate dihydrate	187093
4. 28.		S-(N-2-Cyclooctylethylcarbox-amidinomethyl)thiosulphuric acid	204172AA

Compound No.	Compound Structure	Compound Name	WR No.
42.		N-(2-d,l,isoBornylthioethyl) carboxamidinomethyl disulfide dihydrochloride	204157A
39.		2,2'-Dithiobis-[N-2-(3,5-dimethyl-1-adamantyl)ethyl)acetamidine] dihydrochloride	201727AA
43		1,2'-Dithio-(1-phenyl)-2 N(1-adamantyl)methyl-acetamidine] dihydrochloride	176992AA
19.		2,2'-Dithiobis-[N-2-(1-adamantyl)-ethylacetamidine]dihydrochloride	196264AA

Compound No.	Compound Structure	Compound Name	WR No.
29. 44.		2,2'-Dithiobis-[N-(2-adamantyl) acetamidine]dihydrochloride	196265AA
48.		2,2'-Dithiobis-[N-2-(2-adamantyl)ethyl-acetamidine]dihydrochloride	199270AA
12.		2,2'-Dithiobis-[N-2-(2-thioadamantyl)-ethyl methyl carboxamidine]dihydrochloride	193678AA
18.		2,2'-Dithiobis-[N-2-(1-cyclohexyl) methyl acetamidine]dihydrochloride	193682AA
6.		N-(2-Cyclooctylthioethyl)carboxamidinomethyl disulfide dihydrochloride	204163AA

Compound No.	Compound Structure	Compound Name	WR No.
46.	$[H_2NCH_2CH_2CH_2NHCH_2CH_2S]_2 \cdot H_3PO_4 \cdot H_2O$	Di-2-(3-aminopropylamino)ethyl disulfide monophosphoric acid monohydrate	33278AA
47.	$[CH_3NH(CH_2)_3NHCH_2CH_2S]_2 \cdot 2H_3PO_4$	Di-2-(3-Methylaminopropylamino) ethyl disulfide	183159AA
10. 31.		N-(-Naphthylenemethyl)carboxamidinomethyl disulfide monohydrate hydrochloride	199737AA
22.		N-(1-*cis* Myrtanymethyl)carboxamidinomethyl disulfide dihydrochloride	197487AA
37. 41.		N-(2-iso Bornyl)carboxamidinomethyl disulfide dihydrochloride	199739AA

Compound No.	Compound Structure	Compound Name	WR No.
40.	 ·2HCl	2.2'-Dithiobis[N-(2-cyclohexyl thioethyl)methyl carboxamidino] dihydrochloride	193681AA

UNCLASSIFIED

RESULTS

The antiradiation protective effect was determined for selected compounds employing nearly optimum drug dosage and administration time prior to irradiation. The compounds selected were those found in previous screening studies at WRAIR to provide significant protection. However, minor adjustments in drug dose levels were made to ensure that there were no deaths due to the combined effect of radiation and drug toxicity. For a few of the drugs which showed good protective activity in the initial screening, dose reduction factors were determined by the i.p. route and compared with the DRF found when the drug was given orally.

The number of data points used to calculate the $LD_{50/30}$ values and the confidence limits for each compound are recorded in the Appendix Tables 1 to 48. A summary of the data is presented in Tables I to VIII in which the structure of the compounds is presented with the dosage used and the calculated dose reduction factor. Through Tables I to VIII the compounds have been arranged in accord with their protective activity when the compounds were given orally.

From Table I it is evident substitution in some of the amidine Bunte Salt with 2-cyclohexylethyl, (Compound 1) or 2-cyclooctylthioethyl (Compound 4) did not promote protective activity and substitution of lipid-soluble groups in thiazolidine compounds 2, 3, and 8 was also unsuccessful in providing compounds with significant protective activity. From Tables II and III no chemical structures substituted in the thiazolidine or amidine structure were successful in producing compounds with good protective activity when administered at low drug doses.

From Table IV it can be ascertained that significant protection may be obtained with a variety of structures. It is of interest to note that with compound 21, containing an uncovered thiol group and a substituted adamantyl group, significant protection can be obtained with a dose as low as 30 mg/kg. Also, it is evident that the thiophosphate compound 26 gave a DRF of 1.24 with a dose of 120 mg/kg. The lipid-soluble compound gave protective effect at lower test dose than the water-soluble agent.

In Table V a number of chemical structures are shown which provide positive protection with a drug dose of 100 mg/kg or less (compounds 27, 28, 29, 32 and 33). However, there is no specific structure which provides a satisfactory drug. The lipid-soluble group in compound 34 produced a compound providing protective activity at 50 mg/kg. Compound 35, a water-soluble compound, also provides equivalent protection with a low dose, 75 mg/kg. A number of amidine methyl disulfides, substituted with various lipid-solubilizing groups, provide DRF's of approximately 1.3 with doses less than 200 mg/kg, Table VII. Thus no speicific lipid-solubilizing group appears to be superior although the 3,5-dimethyl-1-adamantyl group provided equal protection with smaller drug dose.

Compounds 44 and 45 provide DRF's of approximately 1.4 when administered in doses of 100 and 75 mg/kg respectively, Table VIII. This demonstrates that the addition of lipid-solubilizing groups to either the disulphide or thiol compounds improves the protective ability of the parent compound.

The polyamine disulphides, compounds 46 and 47, were ineffective as protectors when administered orally.

A few of the better protectors were also given i.p. and DRF's determined to provide a comparison with protection obtained when the compounds were given orally. The screening data are given in the Appendix Tables 49 to 52. A summary of the data is given in Table IX. It is evident that most of the compounds are more effective when administered i.p. Although equivalent DRF's were obtained for compound 44 when administered by either route it required approximately six times more drug when administered orally. In this case the lipid-solubilizing group, although more effective with compound 43 than compounds 19 or 7, was not completely effective in producing a compound which was absorbed effectively by the oral route.

DISCUSSION

Apart from its intrinsic chemical ability to repair a radiation-damaged site, the biologically active protective chemical species can exert its influence only if it can reach the damaged site by a transport process that involves passage through both hydrophilic and lipophilic barriers present in the animal biological system. Thus an important aspect of the design of a drug protective against ionizing-radiation damage is the modification of the hydrophilic character of compounds possessing a desired intrinsic chemical activity so as to optimize their transport to a site most likely to be damaged by ionizing radiation.

One approach used by Westland and his colleagues (4) to increase the lipid solubility and reduce the ionic charge in a potential radioprotective compound was to synthesize a series of N-alkyl-substituted thiazolidines. Preliminary biological screening data indicated that there was a good relationship between chemical structure and protective activity. A few of the best compounds in this series were examined in the present study. From the previous screening data, it was evident that oral dosages of 300 to 400 mg/kg given 15 to 30 min. prior to irradiation were necessary to provide nearly optimum levels of protection. Since the best compound did not provide a DRF value better than 1.45 when a dosage of 300 mg/kg was used it does not appear worthwhile to continue studies in this series.

It would be worthwhile to examine the relationship between chemical structure and protective activity in these compounds synthesized, in an effort to identify chemical structures which promote oral absorption and protective activity. Although the level of protection is not very high in this series of compounds it is evident from Table X that some relationship exists between chemical structure and radioprotection. With reference to the generalized structural formula given in Table X, it may be seen that

when the substituted moiety in the series is X = Br, and Y = O and n = 6 (the number of methylene groups), optimum activity is indicated. Also there does not seem to be any advantage in substituting a chlorine atom for a bromine atom. In comparing the compounds in which the oxygen was replaced by sulphur the DRF value was increased significantly from 1.07 to 1.32 when the side chain contained seven methylene groups. It is also evident that the introduction of the sulphur atom influenced the number of methylene groups which provide optimum protective activity. However the number of methylene groups may be the most important factor because when n = 5, substitution of Br or Cl in the X position and O or S in the Y position did not influence the protective activity.

The protective activity of a large number of the thiazolides has been previously reviewed by Klayman and Copeland (5) and no substituted thiazolidines have been discovered which are effective at low doses. Although Klayman and Copeland (5) commented on the most active compounds as assessed by a one-point screening method no definite chemical structure relationships were deduced. Only in the case of the present investigation and data reported by Farmer, Laung and Luie (6) have dose-reduction factors been determined. It was also evident in the investigation conducted by Farmer et al (6), that no substituted thiazolidines were discovered which provide protection to a DRF of 1.5 or greater when the dose of agent is in the range of 50 to 100 mg/kg.

In the case of the amidine series of compounds $NH_2C(=NH)-CH_2S-$ the

addition of long-chain alkyl groups or large aromatic rings did not promote protective activity. However, the addition of phosphoric or sulphuric acid moieties, or forming a disulphide produced better protective activity. One of the best potential protective agents was synthesized with the addition of dimethyladamantine to the phosphorothioate sodium salt. Therefore, the addition of chemical groups which promote lipid solubility is not always successful in providing a compound with effective protective activity.

From the present results the amidine structure $NH_2-C(=NH)-CH_2S-$ is the most promising basic structure for developing orally effective agents, as those which contain it provide a significant level of protection with lower doses of the agent. Thus the objective of providing protection by oral administration of approximately 50 mg/kg of agents may be met. If similar compounds with higher dose reduction factors can be developed the only remaining problem would be that of pharmacological side effects providing that chemical structures which promote good oral absorption in the mouse also do so in man.

Although it is important from a pharmacological point of view to design a protective agent with a protected thiol group, it may not be so important for the transport process. An example is protection provided by compound 45 which provides a DRF of 1.45 with comparatively low dose of 75 mg/kg. This may be due to the equilibrium between ionized and un-ionized forms of the chemical as the un-ionized form will transport through the lipid barrier faster than the ionized form and the converse is likely for transport through hydrophilic barriers.

Since there are alternative mechanisms for producing protection against ionizing radiation (by chemical repair of damage caused by free radicals (7,8) or by lowering oxygen tension in critical tissue (9)) a few of the compounds were tested in tissue culture by Vos (10) to determine the mechanism of action of the compounds. Compounds 13, 20, 25 were effective protectors in the tissue culture system and therefore the mechanism by which they provide protection is not by the pharmacological action of lowering oxygen tension.

No compounds were discovered to meet the objective of providing a DRF of 2 or greater with an oral dose not exceeding 50 mg/kg. However, the results indicate that the objective could probably be attained as it has been demonstrated that DRF's of approximately 1.5 can be obtained with an oral dose of drug compound 45 of 75 mg/kg.

REFERENCES

1. J.R. Piper, C.R. Stringfellow, Jr., R.D. Elliot and T.P. Johnston, J. Med. Chem. 12, 236 (1969).

2. J.M. Yuhas and J.B. Storer, Int. J. Radiat. Biol. 15, 233 (1969).

3. J.R. Cunningham, W.R. Bruce and H.P. Webb, Phys. Med. Biol., 10, 381 (1965).

4. D.D. Westland, M.M. Merz, S.M. Alexander, L.S. Newton, L. Bauer, T. Conway, J.M. Barton, K.K. Khulleer, B. Devahar and Grenan, M., J. Med. Chem. Vol. 15, 1313, (1972).

5. O.L. Klayman and E.S. Copeland - Drug Design Vol. VI., 81 (1975).

6. P.S. Farmer, C.C. Jeung and Luie, - J. Med. Chem. 16, 411 (1973).

7. G.E. Adam, - Radiation and Sensitization - H.L. Moroson and M. Quintiliani, P. 3, Taylor and Francis, London 1970.

8. G.M. Gaucher, B.L. Mainland, G.P. Thompson, D.A. Armstrong, Radiat. Res. 46, 457 (1971).

9. C. Van der Meer and D.W. van Bekkum, Int. J. Radiat. Biol. 3, 73 (1961).

10. O. Vos, Report to the 9th Meeting of NATO AC/225 Panel VII, Group of Experts on Chemoprophylaxis, November 1976.

TABLE I

Protection Afforded to Mice by Oral Administration

of compounds

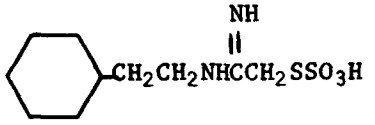
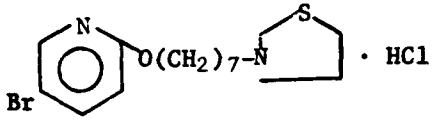
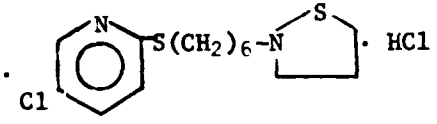
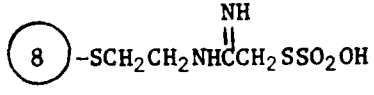
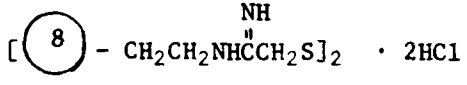
Cpd. No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50/30}$ (rads)	DRF
1.		50	15	762 (704-793)	1.00
2.		300	30	812 (780-837)	1.02
3.		350	15	809 (infinite)	1.02
4.		50	30	829 (817-839)	1.02
5.		50	30	845 (785-830)	1.04

TABLE I (Cont'd)

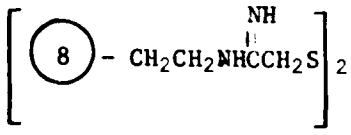
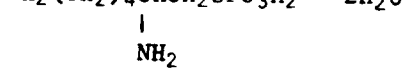
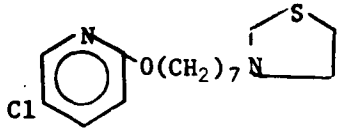
Cpd. No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50}/_{30}$ (rads)	DRF
6.		200	60	822 (792-848)	1.06
7.		500	30	845 (814-867)	1.06
8.		300	30	852 (821-885)	1.07

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TABLE II

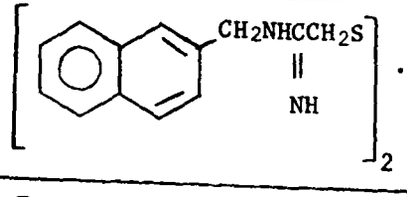
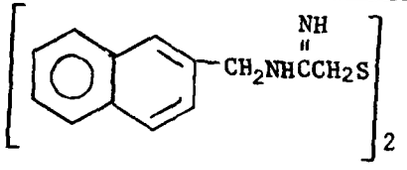
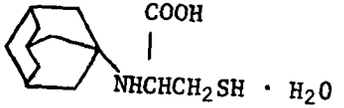
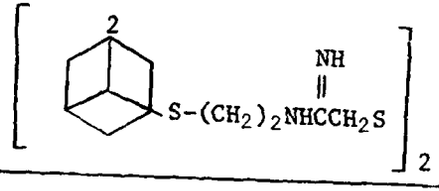
No.	Compound Structure	Oral Dose (mg/kg)	Time (min)	$LD_{50}/_{30}$ (rads)	DRF
9.		100	60	832 (732-962)	1.07
10.		100	30	877 (855-899)	1.08
11.		200	30	890 (871-909)	1.10
12.		50	60	871 (848-894)	1.12
13.	$NH_2(CH_2)_4CHCH_2SPO_3H_2.2H_2O$ (Li) NH_2	300	30	878 (845-904)	1.15

TABLE III

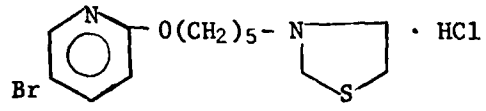
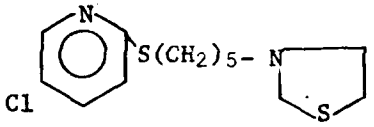
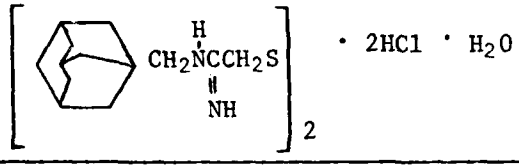
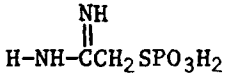
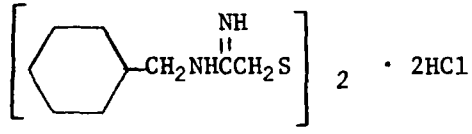
No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50}/_{30}$ (rads)	DRF
14.		400	30	858 (736-980)	1.15
15.		300	30	891 (852-938)	1.15
16.		500	30	901 (856-951)	1.16
17.		120	60	894 (828-963)	1.17
18.		50	60	914 (888-939)	1.17

TABLE III (Cont'd)

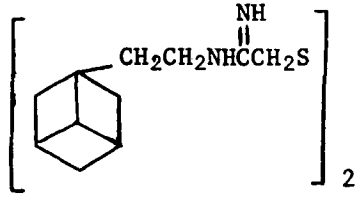
No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50}/_{30}$ (rads)	DRF
19.		50	30	937 (907-966)	1.18

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TABLE IV

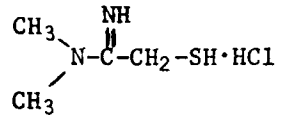
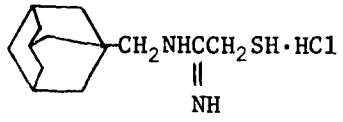
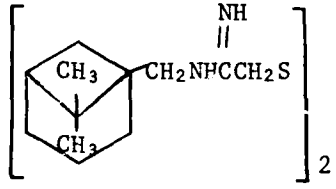
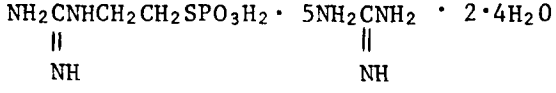
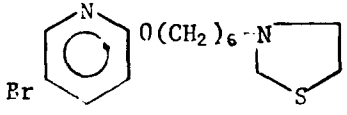
No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50}/_{30}$ (rads)	DRF
20.		175	30	954 (927-978)	1.19
21.		30	30	968 (936-1000)	1.19
22.		100	30	931 (891-968)	1.19
23.		200	30	958 (940-974)	1.20
24.		300	30	947 (872-937)	1.21

TABLE IV (Cont'd)

No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50}/_{30}$ (rads)	DRF
25.	$CH_3NHCH_2CH_2CH_2NH(CH_2)_2SPO_3H_2$	500	60	947 (928-966)	1.22
26.		120	30	1012 (991-1034)	1.24

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TABLE V

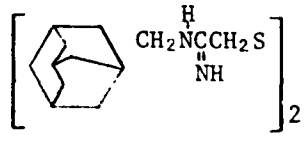
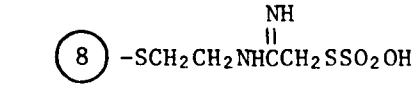
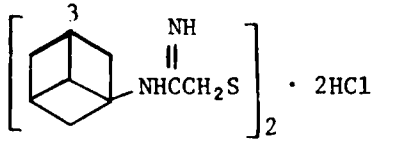
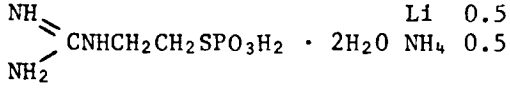
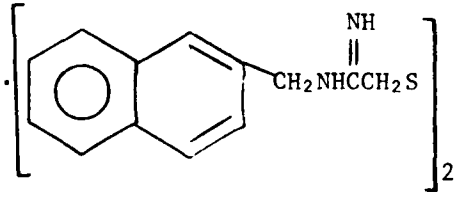
No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50/30}$ (rads)	DRF
27.		100	60	958 (928-986)	1.25
28.		75	60	976 (951-1000)	1.25
29.		100	60	999 (955-1036)	1.26
30.		300	30	1038 (1015-1060)	1.29
31.		150	30	989 (966-1012)	1.29

TABLE V (Cont'd)

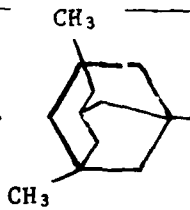
No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50/30}$ (rads)	DRF
32.	 $CH_2NHCCH_2SPO_3HNa \cdot 3H_2O$ (NH)	40	30	1044 (970-1134)	1.30
33.	$NH_2CCH_2SSO_3H$ (NH)	100	30	1040 (1012-1067)	1.30

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TABLE VI

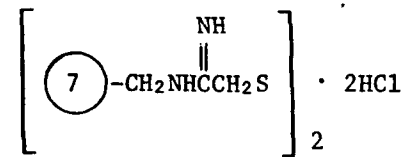
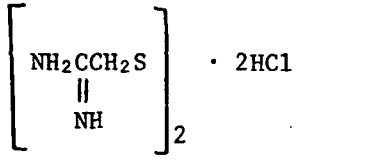
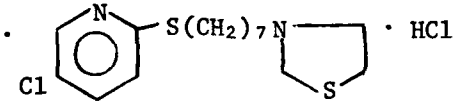
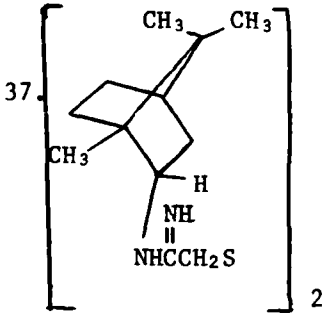
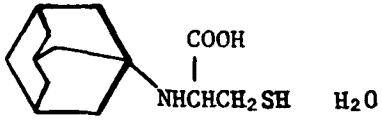
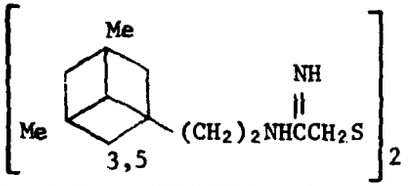
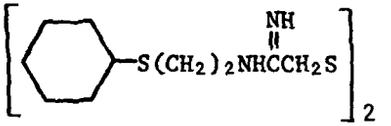
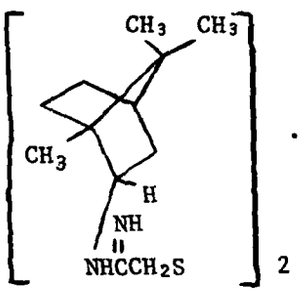
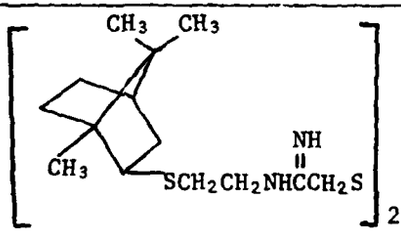
No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50}/_{30}$ (rads)	DRF
34.		50	30	1021 (982-1059)	1.30
35.		75	30	1046 (1012-1080)	1.31
36.		300	30	1029 (905-1161)	1.32
37.		90	30	1076 (1052-1090)	1.32

TABLE VI (Cont'd)

No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50}/_{30}$ (rads)	DRF
38.	 H_2O	400	30	1003 (995-1011)	1.33

UNCLASSIFIED

TABLE VII

No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50}/_{30}$ (rads)	DRF
39.		75	60	1024 (999-1044)	1.34
40.		100	30	1022 (989-1060)	1.35
41.		180	30	1044 (1005-1072)	1.36
42.		120	60	1052 (1041-1063)	1.37

UNCLASSIFIED

TABLE VIII

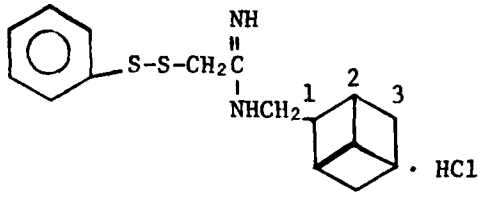
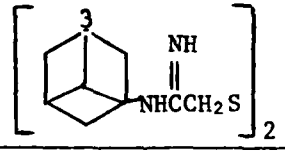
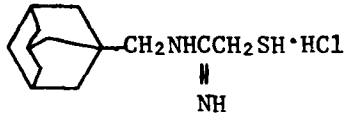
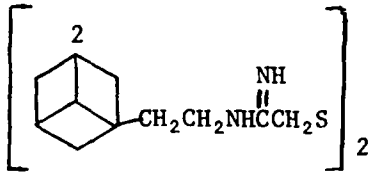
No.	Compound Structure	Oral Dose (mg/kg)	Time (min.)	$LD_{50}/_{30}$ (rads)	DRF
43.		200	30	1063 (972-1210)	1.37
44.		100	30	1093 (1069-1116)	1.43
45.		75	30	1145 (1115-1177)	1.45
46.	$[H_2NCH_2CH_2CH_2NHCH_2CH_2S]_2 \cdot H_3PO_4 \cdot H_2O$	No Protective Effect			
47.	$[CH_3NH(CH_2)_3NHCH_2CH_2S]_2 \cdot 2H_3PO_4$	No Protective Effect			
48.		No Protective Effect			

TABLE IX

Comparison of Protection Afforded to Mice by Intraperitoneal and Oral Administration of a Selected Group of WRAIR Compounds

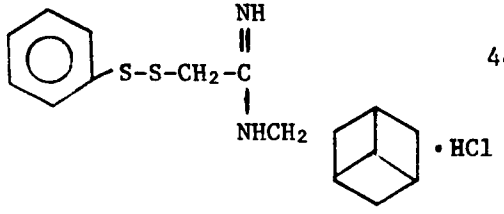
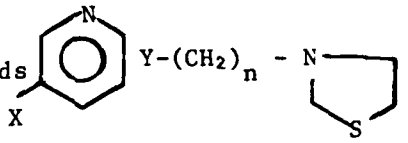
Compound Structure	No.	Dose (mg/kg) I.P.	Dose (mg/kg) Oral	Time (min) I.P.	Time (min) Oral	$LD_{50}/_{30}$ (rad) I.P.	$LD_{50}/_{30}$ (rad) Oral	DRF I.P.	DRF Oral
$CH_3NHCH_2CH_2CH_2NH(CH_2)_2SPO_3H_2$	20	125	500	30	60	1115 (1078-1151)	947	1.43	1.22
	44	30	200	30	30	1145 (1120-1170)	1063 (975-1210)	1.44	1.37
$NH_2(CH_2)_4CH(NH_2)CH_2SPO_3H_2 \cdot 2H_2O$ (Li)	7	200	300	15	30	1265 (1221-1316)	878 (845-902)	1.62	1.15
$NH_2(CH_2)_3CH(NH_2)CH_2SPO_3H_2$ (DL)	-	500	500	60	60	1480 (1429-1545)		1.89	-

TABLE X

Oral Protection provided by the Series of Compounds 

COMPOUND			Oral dose	$LD_{50}/_{30}$ rads	DRF
X	Y	n	mg/kg		
Br	0	5	400	858 (736-980)	1.15
Br	0	6	300	906 (872-937)	1.21
Br	0	7	300	812 (780-837)	1.02
Cl	0	7	300	852 (821-885)	1.07
Cl	S	7	300	1029 (905-1161)	1.32
Cl	S	6	350	809 infinite	1.02
Cl	S	5	300	891 (842-928)	1.15

DRF = dose reduction factor

APPENDIX

TABLE 1

Thirty-day Survival of Mice Treated Orally with 50 mg/kg of WR 4245 AB (Compound 1) 15 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
750	19	7	37
800	20	16	80
900	20	17	85
950	20	20	100

Calculated $LD_{50/30}$ 762 (704 - 793) rads (95% Fiducial Limits)

Slope 8.77 ± 2.20

DRF $\frac{762}{773}$ = 1.00 (0.91 - 1.02)

TABLE 2

Thirty-day Survival of Mice Treated Orally with 300 mg/kg of WR 144975 AB (Compound 2) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
750	20	5	25
800	20	9	45
850	20	13	65
900	20	16	80
950	20	18	90
1000	20	20	100

Calculated $LD_{50/30}$ 812 (780 - 837) rads (95% Fiducial Limits)

Slope 8.97 ± 1.57

DRF $\frac{812}{793}$ = 1.02 (0.98 - 1.05)

TABLE 3

Thirty-day Survival of Mice Treated Orally with 350 mg/kg of WR 132194 AG (Compound 3) 15 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	7	35
850	20	18	80
925	20	18	80
1000	19	19	100

Calculated $LD_{50}/_{30}$ 809 (infinite) (95% Fiducial Limits)

Slope 12.88 ± 7.72

DRF $\frac{809}{793}$ = 1.02

TABLE 4

Thirty-day Survival of Mice Treated Orally with 50 mg/kg of WR 204172 AA (Compound 4) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
775	20	1	5
825	20	8	40
850	20	14	70
875	20	20	100

Calculated $LD_{50}/_{30}$ 829 (817 - 839) rads (95% Fiducial Limits)

Slope 30.41 ± 6.10

DRF $\frac{829}{809}$ = 1.02 (1.00 - 1.04)

TABLE 5

Thirty-day Survival of Mice Treated Orally with 50 mg/kg of WR 199740 AA (Compound 5) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
700	20	1	5
750	20	4	20
800	20	12	60
850	20	13	65
900	19	15	79
950	17	17	100

Calculated $LD_{50/30}$ 807 (785 - 830) rads (95% Fiducial Limits)

Slope 10.30 ± 1.61

DRF $\frac{807}{773}$ = 1.04 (1.01 - 1.07)

TABLE 6

Thirty-day Survival of Mice Treated Orally with 200 mg/kg of WR 204163 AA (Compound 6) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
700	19	1	5
750	20	4	20
800	19	11	58
850	19	12	63
900	20	15	75
950	19	16	84
1000	38	34	89
1050	19	19	100

Calculated $LD_{50/30}$ 822 (793 - 848) rads (95% Fiducial Limits)

Slope 7.56 ± .99

DRF $\frac{822}{774}$ = 1.06 (1.02 - 1.09)

TABLE 7

Thirty-day Survival of Mice Treated Orally with 500 mg/kg of WR 176542 (Compound 7) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	19	4	21
850	20	11	55
900	20	17	85
950	20	18	90
1000	20	19	95

Calculated $LD_{50/30}$ 845 (814 - 867) rads (95% Fiducial Limits)

Slope 11.59 ± 2.26

DRF $\frac{845}{790}$ = 1.06 (1.03 - 1.09)

TABLE 8

Thirty-day Survival of Mice Treated Orally with 300 mg/kg of WR 144976 AB (Compound 8) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
750	20	2	10
800	20	7	35
850	20	11	55
900	20	14	70
975	20	16	80

Calculated $LD_{50/30}$ 852 (821 - 885) rads (95% Fiducial Limits)

Slope 7.76 ± 1.62

DRF $\frac{852}{793}$ = 1.07 (1.03 - 1.11)

TABLE 9

Thirty-day Survival of Mice Treated Orally with 100 mg/kg of WR 197486 AA (Compound 9) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
700	20	1	5
750	20	6	30
800	39	19	49
850	20	6	30
900	20	12	60
950	19	19	100

Calculated $LD_{50/30}$ 832 (732 - 962) rads (95% Fiducial Limits)

Slope 7.43 ± 2.49

DRF $\frac{832}{773}$ = 1.07 (0.94 - 1.24)

TABLE 10

Thirty-day Survival of Mice Treated Orally with 100 mg/kg of WR 199737 AA (Compound 10) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
750	20	2	10
800	20	3	15
850	20	5	25
900	20	12	60
950	20	17	85
1000	20	18	90
1050	20	20	100

Calculated $LD_{50/30}$ 877 (855-899) rads (95% Fiducial Limits)

Slope 10.72 ± 1.48

DRF $\frac{877}{809}$ = 1.08 (1.05 - 1.11)

TABLE 11

Thirty-day Survival of Mice Treated Orally with 200 mg/kg of WR 190205 AB (Compound 11) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
750	20	0	0
800	20	2	10
850	20	5	25
900	20	8	40
950	20	19	95
1000	20	19	95
1100	20	20	100

Calculated $LD_{50/30}$ 890 (871 - 909) rads (95% Fiducial Limits)

Slope 14.82 ± 2.16

DRF $\frac{890}{803}$ = 1.10 (1.08 - 1.13)

TABLE 12

Thirty-day Survival of Mice Treated Orally with 150 mg/kg of WR 193678 AA (Compound 12) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
750	20	1	5
800	20	5	25
850	20	9	45
900	20	8	40
950	20	17	85
1000	20	20	100

Calculated $LD_{50/30}$ 871 (848 - 894) rads (95% Fiducial Limits)

Slope 10.58 ± 1.63

DRF $\frac{871}{774}$ = 1.12 (1.09 - 1.15)

TABLE 13

Thirty-day Survival of Mice Treated Orally with 300 mg/kg of WR 187093 (Compound 13) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	6	30
850	20	7	35
880	20	8	40
950	20	17	85
1000	40	32	80
1050	20	20	100

Calculated $LD_{50/30}$ 878 (845 - 904) rads (95% Fiducial Limits)

Slope 8.25 ± 1.38

DRF $\frac{878}{763}$ = 1.15) 1.10 - 1.19)

TABLE 14

Thirty-day Survival of Mice Treated Orally with 400 mg/kg of WR 43898 AD (Compound 14) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	6	30
850	40	14	35
900	20	14	70
950	20	20	100

Calculated $LD_{50/30}$ 858 (736 - 989) rads (95% Fiducial Limits)

Slope 13.35 ± 4.81

DRF $\frac{858}{741}$ = 1.15 (0.99 - 1.33)

TABLE 15

Thirty-day Survival of Mice Treated Orally with 300 mg/kg of WR 126455 AB (Compound 15) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
750	20	1	5
800	20	7	35
900	20	10	50
950	20	15	75
1000	20	15	75
1050	20	16	80

Calculated $LD_{50/30}$ 891 (852 - 928) rads (95% Fiducial Limits)

Slope 6.70 ± 1.13

DRF $\frac{891.0}{769}$ = 1.15 (1.10 - 1.20)

TABLE 16

Thirty-day Survival of Mice Treated Orally with 500 mg/kg of WR 155419 AB (Compound 16) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	6	30
850	20	7	35
900	20	8	40
950	20	12	60
1000	20	16	80

Calculated $LD_{50/30}$ 901 (856 - 951) rads

Slope 5.88 ± 1.70

DRF $\frac{901}{773}$ = 1.16 (1.10 - 1.23)

TABLE 17

Thirty-day Survival of Mice Treated Orally with 120 mg/kg of WR 108250 AB (Compound 17) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
750	20	0	0
800	20	1	5
850	20	11	55
900	20	12	60
950	20	16	80
1075	20	18	90
1150	20	18	90
1225	19	19	100

Calculated $LD_{50/30}$ 894 (828 - 963) rads (95% Fiducial Limits)

Slope 7.88 ± 1.75

DRF $\frac{894}{773}$ = 1.16 (1.07 - 1.25)

TABLE 18

Thirty-day Survival of Mice Treated Orally with 50 mg/kg of WR 193682 AA (Compound 18) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	1	5
850	20	6	30
880	20	6	30
950	20	15	75
1000	20	17	85
1050	19	17	89
1100	20	18	90

Calculated $LD_{50/30}$ 914 (888 - 939) rads (95% Fiducial Limits)

Slope 9.27 ± 1.34

DRF $\frac{914}{775}$ = 1.17 (1.14 - 1.21)

TABLE 19

Thirty-Day Survival of Mice Treated Orally with 50 mg/kg of WR 196264AA (Compound 19) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	2	10
850	20	6	30
900	20	6	30
950	20	11	55
1000	20	14	70
1050	20	14	70
1100	20	19	100

Calculated $LD_{50/30}$ 937 (907-966) rads (95% Fiducial Limits)

Slope 7.89 ± 1.25

DRF $\frac{937}{793}$ = 1.18 (1.14 - 1.21)

TABLE 20

Thirty-Day Survival of Mice Treated Orally with 175 mg/kg of WR 76841 AB (Compound 20) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
825	20	1	5
900	20	4	20
975	20	13	65
1025	20	16	80
1100	20	19	95
1175	20	20	100

Calculated $LD_{50/30}$ 954 (927-978) rads (95% Fiducial Limits)

Slope 12.23 ± 1.88

DRF $\frac{953.5}{796}$ = 1.19 (1.16 - 1.22)

TABLE 21

Thirty-Day Survival of Mice Treated Orally with 30 mg/kg of WR 109342 AC (Compound 21) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	4	20
900	20	6	30
950	20	7	35
1000	20	12	60
1050	20	13	65
1100	20	19	95

Calculated $LD_{50/30}$ 968 (936-1000) rads (95% Fiducial Limits)

Slope 7.95 ± 1.51

DRF $\frac{968}{807.0}$ = 1.19 (1.15 - 1.23)

TABLE 22

Thirty-Day Survival of Mice Treated Orally with 100 mg/kg of WR 197487 AA (Compound 22) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	2	10
850	20	4	20
900	18	11	61
1050	18	14	78
1100	18	15	83
1150	18	17	94
1200	16	15	94

Calculated $LD_{50/30}$ 931 (891-968) rads (95% Fiducial Limit)

Slope 6.76 ± 0.98

DRF $\frac{931}{777}$ = 1.19 (1.14 - 1.24)

TABLE 23

Thirty-Day Survival of Mice Treated Orally with 200 mg/kg of WR176240 AB (Compound 23) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	0	0
900	39	12	31
950	40	16	40
1000	40	33	83
1050	40	32	80
1100	40	36	90
1150	20	20	100

Calculated $LD_{50/30}$ 958 (940-974) rads (95% Fiducial Limits)

Slope 11.19 ± 1.29

DRF $\frac{958}{796}$ = 1.20 (1.18 - 1.22)

TABLE 24

Thirty-Day Survival of Mice Treated Orally with 300 mg/kg of WR 91496 AD (Compound 24) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	3	15
850	20	6	30
925	20	13	65
1000	20	14	70
1075	20	18	90
1150	20	20	100

Calculated $LD_{50/30}$ 906 (872-937) rads (95% Fiducial Limits)

Slope 8.04 ± 1.28

DRF $\frac{906}{749}$ = 1.21 (1.16 - 1.25)

TABLE 25

Thirty-Day Survival of Mice Treated Orally with 500 mg/kg of WR 3689 AD (Compound 25) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	0	0
850	20	1	5
900	19	6	32
950	20	8	40
1000	20	16	80
1050	20	19	95
1100	20	20	100

Calculated $LD_{50/30}$ 947 (928-966) rads (95% Fiducial Limits)

Slope 15.18 ± 2.10

DRF $\frac{947}{774}$ = 1.22 (1.20 - 1.25)

TABLE 26

Thirty-Day Survival of Mice Treated Orally with 120 mg/kg of WR 108250 AB (Compound 26) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
900	20	0	0
950	20	5	25
1000	20	9	45
1050	20	13	65
1100	20	18	90

Calculated $LD_{50/30}$ 1012 (991-1034) rads (95% Fiducial Limits)

Slope 14.72 ± 2.50

DRF $\frac{1012}{817}$ = 1.24 (1.21 - 1.27)

TABLE 27

Thirty-Day Survival of Mice Treated Orally with 100 mg/kg of WR 155419 AB (Compound 27) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	1	5
850	20	3	15
950	20	9	45
1000	20	14	60
1050	19	14	74
1100	20	17	85
1150	20	20	100

Calculated $LD_{50/30}$ 958 (928-986) rads (95% Fiducial Limits)

Slope 9.00 ± 1.26

DRF $\frac{958}{763}$ = 1.25 (1.21 - 1.29)

TABLE 28

Thirty-Day Survival of Mice Treated Orally with 75 mg/kg of WR 204172 AA (Compound 28) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	1	5
900	20	4	20
928	20	8	40
1000	20	9	45
1050	20	17	85
1100	20	17	85
1150	20	20	100

Calculated $LD_{50/30}$ 976 (951-1000) rads (95% Fiducial Limits)

Slope 10.63 ± 1.47

DRF $\frac{976}{775}$ = 1.25 (1.22 - 1.29)

TABLE 29

Thirty-Day Survival of Mice Treated Orally with 100 mg/kg of WR 196265 AA (Compound 29) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	3	15
900	19	3	16
950	19	11	58
1050	39	27	69
1100	40	26	65
1150	20	13	65
1200	20	18	90

Calculated $LD_{50/30}$ 999 (955-1036) rads (95% Fiducial Limits)

Slope 5.49 ± 0.97

DRF $\frac{999}{787}$ = 1.26 (1.21 - 1.31)

TABLE 30

Thirty-Day Survival of Mice Treated Orally with 300 mg/kg of WR 180152 (Compound 30) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	0	0
950	20	3	15
1000	20	4	20
1050	20	14	70
1100	20	14	70
1150	20	19	95
1200	20	19	95
1250	20	19	100

Calculated $LD_{50/30}$ 1038 (1015-1060) rads (95% Fiducial Limits)

Slope 13.35 ± 1.83

DRF $\frac{1038}{803}$ = 1.29 (1.26 - 1.32)

TABLE 31

Thirty-Day Survival of Mice Treated Orally with 150 mg/kg of WR 199737 AA (Compound 31) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	1	5
900	20	2	10
950	20	8	40
1000	20	11	55
1050	20	14	70
1100	20	17	85
1150	20	20	100

Calculated $LD_{50/30}$ 989 (966-1012) rads (95% Fiducial Limits)

Slope 11.35 ± 1.57

DRF $\frac{989}{763}$ = 1.29 (1.26 - 1.32)

TABLE 32

Thirty-Day Survival of Mice Treated Orally with 40 mg/kg of WR 159243 AB (Compound 32) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	0	0
850	20	1	5
900	19	6	32
1000	39	10	26
1075	20	10	50
1150	20	15	75
1200	19	19	100

Calculated $LD_{50/30}$ 1044 (970-1134) rads (95% Fiducial Limits)

Slope 7.86 ± 1.81

DRF $\frac{1044}{803}$ = 1.30 (1.21 - 1.41)

TABLE 33

Thirty-Day Survival of Mice Treated Orally with 100 mg/kg of WR 1551 AD (Compound 33) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
750	20	0	0
850	18	1	6
950	39	9	23
975	20	6	30
1050	20	10	50
1100	20	13	65
1150	39	34	87

Calculated $LD_{50/30}$ 1044 (1012-1067) rads (95% Fiducial Limits)

Slope 8.17 ± 1.09

DRF $\frac{1044}{796}$ = 1.30 (1.27 - 1.34)

TABLE 34

Thirty-Day Survival of Mice Treated Orally with 50 mg/kg of WR 151331 AB (Compound 34) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	19	2	10
900	20	2	10
950	20	9	45
1000	40	23	58
1100	40	26	65
1150	20	13	65
1200	20	16	80

Calculated $LD_{50/30}$ 1021 (982-1059) rads

Slope 5.53 ± 0.97

DRF $\frac{1021}{785}$ = 1.30 (1.25 - 1.35)

TABLE 35

Thirty-Day Survival of Mice Treated Orally with 75 mg/kg of WR 33763 AD (Compound 35) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	1	5
900	20	2	10
950	20	5	25
1000	20	8	40
1050	20	12	60
1100	20	15	75
1150	20	17	85
1250	39	31	79
1375	20	18	90
1400	20	20	100

Calculated $LD_{50/30}$ 1046 (1012-1080) rads (95% Fiducial Limits)

Slope 6.40 ± 0.75

DRF $\frac{1046}{796}$ = 1.31 (1.27 - 1.36)

TABLE 36

Thirty-Day Survival of Mice Treated Orally with 300 mg/kg of WR 158490 AB (Compound 36) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
900	20	0	0
900	20	4	20
1050	20	8	40
1100	20	17	85
1200	20	20	100

Calculated $LD_{50/30}$ 1029 (905-1161) rads (95% Fiducial Limits)

Slope 10.37 ± 3.21

DRF $\frac{1029}{777}$ = 1.32 (1.16 - 1.49)

TABLE 37

Thirty-Day Survival of Mice Treated Orally with 90 mg/kg of WR 199739 AA (Compound 37) 30 min Prior to Irradiation

Dose (rads)	No. Of Mice	No. Dead	Percent Mortality
900	20	0	0
1000	20	4	20
1050	20	8	40
1100	20	10	50
1150	20	16	80
1200	20	20	100

Calculated $LD_{50/30}$ 1076 (1052-1098) rads (95% Fiducial Limits)

Slope 14.25 ± 2.32

DRF $\frac{1076}{809}$ = 1.32 (1.30 - 1.35)

TABLE 38

Thirty-Day Survival of Mice Treated Orally with 400 mg/kg of WR 190205 AA (Compound 38) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	0	0
900	34	6	18
950	20	9	45
1000	20	10	50
1050	20	11	55
1100	20	15	75
1200	20	20	100

Calculated $LD_{50/30}$ 1003 (995-1011) rads (95% Fiducial Limits)

Slope 9.36 ± 1.31

DRF $\frac{1003}{753}$ = 1.33 (1.32 - 1.34)

TABLE 39

Thirty-Day Survival of Mice Treated Orally with 75 mg/kg of WR 201727 AA (Compound 39) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	0	0
900	20	2	10
1000	20	4	20
1050	20	12	60
1100	38	34	89
1150	19	19	100
1200	20	19	95

Calculated $LD_{50/30}$ 1024 (999-1044) rads (95% Fiducial Limits)

Slope 13.76 ± 1.94

DRF $\frac{1024}{763}$ = 1.34 (1.30 - 1.37)

TABLE 40

Thirty-Day Survival of Mice Treated Orally with 100 mg/kg of WR 193681 AA (Compound 40) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	19	1	5
850	19	1	5
900	20	7	35
950	20	7	35
1000	20	9	45
1050	19	10	53
1100	19	9	47
1150	20	16	80
1200	19	18	95

Calculated $LD_{50/30}$ 1022 (989-1060) rads (95% Fiducial Limits)

Slope 6.32 ± 0.92

DRF $\frac{1022}{753}$ = 1.35 (1.31 - 1.40)

TABLE 41

Thirty-Day Survival of Mice Treated Orally with 180 mg/kg of WR 199739 AA (Compound 41) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
1000	18	6	33
1050	17	9	53
1100	19	13	68
1200	19	18	95
1250	20	20	100

Calculated $LD_{50/30}$ 1044 (1005-1072) rads (95% Fiducial Limits)*

Slope 11.95 ± 2.49

DRF $\frac{1044}{763}$ = 1.36 (1.31 - 1.40)

* Including some early deaths.

TABLE 42

Thirty-Day Survival of Mice Treated Orally with 120 mg/kg of WR 204157 A (Compound 42) 60 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
800	20	1	5
850	20	1	5
950	20	5	25
1000	20	9	45
1050	20	11	55
1100	20	13	65
1150	20	12	60
1200	20	15	75
1250	20	17	85
1300	20	19	95

Calculated $LD_{50/30}$ 1052 (1041-1063) rads (95% Fiducial Limits)

Slope 6.23 ± 0.80

DRF $\frac{1052}{763}$ = 1.37 (1.36 - 1.39)

TABLE 43

Thirty-Day Survival of Mice Treated Orally with 200 mg/kg of WR 176992 AA (Compound 43) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	19	0	0
900	19	3	16
950	19	5	26
1000	18	4	22
1050	18	6	33
1100	18	7	39
1150	18	18	100

Calculated $LD_{50/30}$ 1063 (973-1210) rads (95% Fiducial Limits)

Slope 8.47 ± 2.59

DRF $\frac{1063}{775}$ = 1.37 (1.25 - 1.56)

TABLE 44

Thirty-Day Survival of Mice Treated Orally with 100 mg/kg of WR 19625 AA (Compound 44) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
850	20	1	5
900	20	1	5
950	20	2	10
1000	20	4	20
1050	20	3	15
1100	20	9	45
1150	38	26	68
1200	20	16	80
1250	19	18	95
1300	39	39	100

Calculated $LD_{50/30}$ 1093 (1069-1116) rads (95% Fiducial Limits)

Slope 9.89 ± 1.07

DRF $\frac{1093}{763}$ = 1.43 (1.40 - 1.46)

TABLE 45

Thirty-Day Survival of Mice Treated Orally with 75 mg/kg of WR 109342 AA (Compound 45) 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
900	20	0	0
950	20	1	5
1000	20	4	20
1100	20	5	25
1150	20	10	50
1200	20	13	65
1250	20	15	75
1300	20	19	95

Calculated $LD_{50/30}$ 1145 (1115-1177) rads (95% Fiducial Limits)

Slope 9.05 ± 1.25

DRF $\frac{1145}{787}$ = 1.45 (1.41 - 1.49)

TABLE 46

Thirty-Day Survival of Mice Treated Orally with 300 mg/kg and 500 mg/kg of WR 33278 AA (Compound 46) and Irradiated with 900 rads 30 and 60 min After Injection

Time (min)	No. of Mice	No. Dead	Percent Mortality
	300 mg/kg + 900 rads		
30	20	20	100
60	20	20	100
	500 mg/kg + 900 rads		
30	20	18	90
60	20	20	100

Compound seems to show no protective effect.

No toxic deaths with compound up to 500 mg/kg with no irradiation.

TABLE 47

Thirty-Day Survival of Mice Treated Orally with 500 mg/kg of WR 183159 AA (Compound 47) and Irradiated with 900 rads at Various Times After Injection

Time (min)	No. of Mice	No. Dead	Percent Mortality
30	20	20	100
60	20	20	100
90	20	20	100

Compound seems to show no protective effect.

No toxic deaths with compound up to 500 mg/kg with no irradiation.

TABLE 48

Thirty-Day Survival of Mice Treated Orally with 100,75 and 50 mg/kg of WR 199270 AA (Compound 48) and Irradiated with 900 rads 30 min After Injection

Time (min)	No. of Mice	No. Dead	Percent Mortality
	100 mg/kg + 900 rads		
30	19	15	79
	75 mg/kg + 900 rads		
30	15	15	100
	50 mg/kg + 900 rads		
30	16	16	100

Compound seems to show no protective effect.

No toxic deaths with compound up to 300 mg/kg with no irradiation.

TABLE 49

Thirty-Day Survival of Mice Treated Intraperitoneally with 125 mg/kg of WR 3689 AD 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
900	20	0	0
1000	20	6	30
1100	20	6	30
1200	20	13	65
1300	20	20	100
1400	20	20	100

Calculated $LD_{50/30}$ 1115 (1078 - 1151) rads (95% Fiducial Limits)

Slope 9.69 ± 1.40

DRF $\frac{1115}{777}$ = 1.43 (1.39 - 1.48)

TABLE 50

Thirty-Day Survival of Mice Treated Intraperitoneally with 30 mg/kg of WR 176992AA 30 min Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
950	19	0	0
1000	20	3	15
1050	20	3	15
1100	19	5	26
1150	20	10	50
1200	20	11	55
1250	20	18	90
1300	20	20	100

Calculated $LD_{50/30}$ 1145 (1120 - 1170) rads (95% Fiducial Limits)

Slope 11.45 ± 1.52

DRF = $\frac{1145}{793}$ 1.44 (1.41 - 1.47)

TABLE 51

Thirty-day Survival of Mice Treated Intraperitoneally with 200 mg/kg of WR 187093 15 min. Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
950	20	0	0
1000	20	2	10
1100	20	3	15
1200	20	5	25
1300	20	11	55
1400	15	13	87
1500	20	18	90

Calculated $LD_{50}/_{30}$ 1265 (1221-1316) rads (95% Fiducial Limits)

Slope 7.52 ± 1.04

DRF $\frac{1265}{777} = 1.62$ (1.57-1.69)

TABLE 52

Thirty-day Survival of Mice Treated Intraperitoneally with 200 mg/kg of WR 179209 60 min. Prior to Irradiation

Dose (rads)	No. of Mice	No. Dead	Percent Mortality
1000	20	0	0
1050	20	1	5
1100	20	1	5
1150	20	1	5
1200	20	1	5
1300	20	2	10
1400	20	7	35
1500	20	11	55
1600	20	13	65
1700	20	18	90

Calculated $LD_{50}/_{30}$ 1480 (1429-1545) rads

Slope - 6.61 ± 0.85

DRF $\frac{1480}{785}$ = 1.89 (1.82-1.97)

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13. ABSTRACT

Forty-two compounds previously screened at the Walter Reed Army Institute of Research were selected for further evaluation. The compounds were administered orally to mice prior to gamma irradiation. The $LD_{50/30}$ was computed and dose reduction factors determined. Dose reduction factors up to 1.45 were obtained for both water- and lipid-soluble compounds with administered oral doses of 100 mg/kg or less. The relationship between chemical structure and protective activity of the compounds is discussed.

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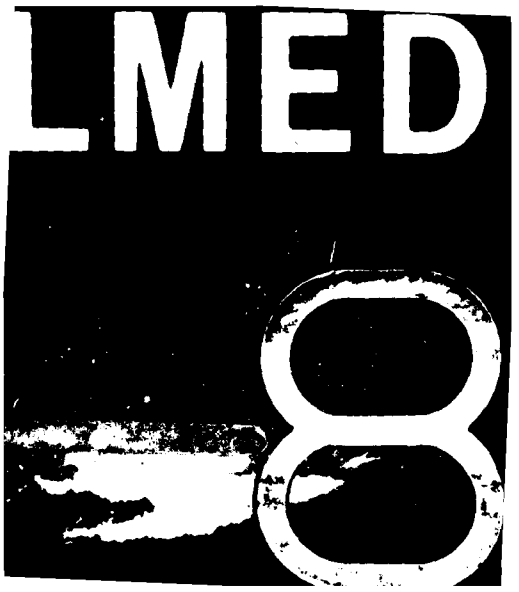
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